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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,017	08/02/2001	Gregory S. Hamilton	AR762-XXA	7616

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GUILFORD PHARMACEUTICALS C/O
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EXAMINER

CHANG, CELIA C

ART UNIT	PAPER NUMBER
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1625

DATE MAILED: 12/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/920,017

Applicant(s)

HAMILTON ET AL.

Examiner

Celia Chang

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 06 October 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-82 is/are pending in the application.
- 4a) Of the above claim(s) 4, 12 and 14-82 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-3 and 5-11, 13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3-9, 12.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. Applicant's election with traverse of Group I claims 6-7 and species of compound 30 as the elected species in Paper No. 14, dated Oct. 16, 2002 is acknowledged. The traversal is on the ground(s) that "the Office has improperly required restriction between groups I and II because these two groups contain claims that are Markush-type claims.....". This is not persuasive.

Applicants argued that MPEP803.02 Markush practice indicated that

"Broadly, unity of invention exists where compounds included within a Markush group (1)share a common utility *and* (2)share a substantial structural feature disclosed as being essential to that utility"

Please note that group I and group II compounds do not share *any* structural commonality due to lacking of common "core". Group I is drawn to 5-membered ring compounds while group II is drawn to 6-membered ring compounds. Lacking of a common core is one of the criteria for restriction. In re Harnish 206 USPQ 300.

Further, it is evidence in the prior art that the 5-membered ring compounds (see CA 83079-95-2, 83079-96-3, 53935-75-4 all cited on 1449) have angiotension converting enzyme inhibiting use or being activated pyruvic acid compounds while the 6-membered ring compounds have analgesic (CA 91:168360, 94:47062) of protease inhibitor activity (see Kitazaki cited on 1449). Therefore, art of record evidenced that not only the compounds lacks common structural feature, group I and group II core also have different utility.

In addition, please note that the restriction was the identical restriction as made in the parent application for which the n=3 compounds were elected and allowed. Applicants provided not factual evidence as to show why unity of invention was applicable to part of Markush, namely n=1 and 2 compounds but not applicable to the n=3 compounds. Based on the factual evidenced provided by the prior art, the n=1, n=2, n=3 compounds having distinct "core" structure with distinct utility of each core are improper Markush format and restriction is proper.

Further, for each group of compounds, a species election was also required. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious

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variants or clearly admit on the record that this is the case, for which applicants provided neither evidence nor admission. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 10-3(a) of the other invention. In the instant case, were applicants argued that all the species are prima facie obvious of each other or clearly admit on the record that this is the case, then, there could have been no patentability of all the claims over Bycroft et al. CA 84:106021, see RN 58885-83-9 which anticipated claims 1 and 4.

The requirement is still deemed proper and is therefore made FINAL.

Based on the election of Group I and compound 30, claims 6-7, and generic claims 1-3, 5, 8-11, 13 reading on R₂ is heterocycle of claim 3 is prosecuted. Claims 4, 12, 14-82 are withdrawn from consideration per 37 CFR 1.142(b).

2. Claim 1, 2, 5, 6, 10, 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is ambiguous. It is very confusing on pages 121-123 with an enormous proviso conditions. It is unclear as to what is in and what is out i.e. whether all the provisos are operating simultaneously or one at a time etc. It is recommended that applicants limit the claim to the elected invention and claim *what is* applicants' invention instead of what is *not* applicants' invention.

Claim 2 and 10 are self-conflicting because claim 2 has the scope that "R₂ is carbocycle..... containing CH₂," which will not include phenyl yet on page 125, the R₂ moiety was either phenyl or phenyl tautomer.

Claims 5 and 13 are improper under modern claim practice. Please note that claims must under modern claim practice stand alone to define invention and incorporation into claims by express reference to specification is not permitted. See Ex parte Fressola 27 USPQ2d 1608. There is not reason why the names of the compound cannot be clearly named in claims. It is recommended that those compounds reading on the election be explicitly claimed by its name or structural formula.

It is unclear "what" is the structure of claim 6. If this is compound 143 on page 62, the nomenclature does not read on this compound. Clarification is required.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Bycroft et al. CA 84:106021. See RN 58885-83-9 anticipated the claims. Deletion of the non-elected invention is recommended.

Claims 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Gold et al. US 4,818,749, see col. 5 example 1, cline 9-10, Burbaum et al. US 5,319,098, see col. 5 lines 40-60, Hamilton et al. US 6,291,510, see col. 15 lines 4-5. Each marked section of the reference disclosed pyruvateproline in composition with pharmaceutically acceptable organic solvent carrier, which anticipated the compositions. Deletion of the non-elected invention is recommended.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(f) he did not himself invent the subject matter sought to be patented.

Claims 1-3, 5, 8-11, 13 are rejected under 35 U.S.C. 102(f) as being anticipated by WO 99/14998.

WO 99/14998 is a reference by "another" that has disclosed compounds anticipated the claims including species of claim 5 and 13. Because it is evidenced that WO 99/14998 has a US filing date prior to applicant's provisional filing date, this evidence indicated that applicants are not the first to invent since "another" was in possession of the claims.

The US provisional of WO 99/14998 upon issuance can also be a provisional 102 (e) or (g) reference based on the priority and disclosure of the provisional applications of WO 99/14998.

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5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

(f) he did not himself invent the subject matter sought to be patented.

(g)(1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or (2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Claims 1-2, 6-10 are rejected under 35 U.S.C. 102(e), (f), or (g) as being anticipated by Brumby et al. US 6,284,779 or Kata et al. CA 135:226999 supplemented with Andersen et al. CA 121:300841.

Claims 1-2, 6-10 according to the election of $n=1$ compounds are pyrrolidinyl compounds with a dioxo- moiety at the 1-position and direct or indirect attachment at the 2-position of “a carboxylic acid or carboxylic acid isostere”. Both Brumby and Kata disclosed such compounds wherein the 2-position is a carboxylic acid isostere as evidence by Andersen et al. that unsubstituted as well as substituted oxadiazol moieties are considered bioisosteres for the carboxylic functionality. Since the species of Brumby et al. (col. 12, example 2) or Kata et al. (see RN 359802-65-6 etc. attached) anticipated the instant generic claims, yet applicants' disclosure lacks the species of the specific oxadiazolyl moieties of Brumby et al. or Kata et al., applicants' genus lacks descriptive/enabling support for the species of Brumby or Kata, thus, a 102(e) or (f) (against instant claims 1-2, 8-10) or (g) (against instant claims 6-7) date is proper. Please note that the term “carboxylic acid isostere” encompassed any structural isosteric moieties even those not called but functions in such manner such as those disclosed by Brumby or Kata, including generically the halosubstituted phenyl or methyl substituted five membered rings (see Brumby col 4, R4 is alkyl or Ar substituted by E=halogen) of instant claims 6-7.

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6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, and 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamilton US 5,859,031 (cited on 1449), US 5,945,441, US 6,177,455, US 6,291,510 in view of Silverman or Bungaard further in view of Li et al. US 5,801,187 (cited on 1449) and Li et al. US 6,218,544.

Determination of the scope and content of the prior art (MPEP §2141.01)

Hamilton '031, '441, '445, '510 disclosed pyrrolidinyl compounds with 1-dioxolyl substitution and 2- carboxylic ester and their compositions which have identical utility as the instantly claims i.e. neurotrophic/immunophillin inhibitors.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Hamilton '031, '441, '445, '510 disclosed all the elements of the claims **except** the compounds are in form of an ester of the instant carboxylic acid or carboxylic acid isostere. Bungaard taught that ester is a "prodrug" of free carboxylic acid compounds since naturally, under physiological conditions, the ester will be hydrolyzed to acid by esterases which can be found in the blood, liver and other organs or tissues (see Bungaard p.3-4 para bridging) while Silverman taught the same concept further taught the same approach can be extend to sulfate or phosphate esters (see p.356) and the modification of the ester moiety to increase the hydrolyzation rate (see p.357). Li et al. '187 and '544 evidenced that the general approach taught by Bungaard or Silverman is applicable to the field of small molecules having neurotrophic/immunophillin inhibitors analogous to the instantly claimed compounds.

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art is deemed to be aware of all the pertinent art in the field. The above references placed the prodrug and how such prodrug functions physiologically in the possession of artisan in the field. One skilled in the art in possession of the Hamilton '031, '441, '445, '510 is tantamount to in possession of the instant claims **because** the mechanism of how a prodrug functions through the drug can not be separated from the drug per se. Further, it is evidenced in the art that both the free carboxylic acid (see Li '544, col. 14, claim 1) and the ester (see Li '187, col. 13-14 claims 1-12) functions analogously. No evidence in the record indicated that the esters of Hamilton '031, '441, '445, '510 should not function in physiological conditions according to common knowledge of the art as taught by Bungaard or Silverman.

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7. Claims 1-3, 8-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 18 of U.S. Patent No. 5,859,031, claim 4, of U. S. Patent no. 6,291,510 in view of Silverman or Bungaard further in view of claims 1-8 of Li et al. US 5,801,187 (cited on 1449) and claim 1 of Li et al. Us 6,218,544.

The same rational as section 6 of finding the claims prima facie obvious is applicable and hereby incorporated by reference.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

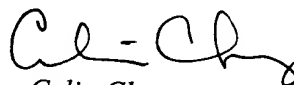
8. The corrected or substitute drawings were received on Oct. 16, 2002. These drawings are not acceptable by the draftsman and the PTO-948 is attached.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is 703-308-4702. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner can be reached by facsimile at (703) 308-7922 with courtesy voice message supra.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

OACS/Chang
Dec. 5, 2002


Celia Chang
Primary Examiner
Art Unit 1625